



ARTICLE

Imaging of thymic disorders

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Date accepted for publication 2 August 2005

Abstract

Evaluation of the thymus poses a challenge to the radiologist. In addition to age-related changes in thymic size, shape, and tissue composition, there is considerable variability in the normal adult thymic appearance within any age group. Many different types of disorders may affect the thymus, including hyperplasia, cysts, and benign and malignant neoplasms, both primary and secondary; clinical and imaging findings typical for each disease process are described in this article. Whereas computed tomography is the mainstay for imaging the thymus, other imaging modalities may occasionally provide additional structural or functional information.

Keywords: Thymus; imaging.

Normal thymus

The normal thymus is a triangular, bilobed organ residing in the anterior mediastinum; its shape, size and composition changes with age^[1]. There is great variability in the appearance of the thymus on imaging studies, including features such as size, shape, attenuation on computed tomography (CT) and signal characteristics on, magnetic resonance imaging (MRI). Due to the variety of imaging appearances, it may be challenging to differentiate the normal from the diseased thymus^[1,2].

The thymus acquires its adult, triangular shape in late childhood or adolescence, a shape often best appreciated on coronal images (Fig. 1). The left lobe is often slightly more prominent than the right, with concave or flat margins in the normal adult^[1]. Fatty infiltration begins in childhood, with a gradual decline in CT attenuation, starting at the age of approximately 1 year^[3]; the originally homogenous thymic soft tissue gradually involutes and becomes replaced by fat. By the age of 40, the thymus is usually mostly fatty in composition, although it may contain speckles of soft tissue (Fig. 2)^[4]. However, there is considerable variability in the rate of involution of the thymus, and thymic remnant tissue

is commonly seen in patients in their forties and even sometimes in their fifties. On T1-weighted MR images (T1WI), adult thymic signal intensity is generally slightly greater than muscle but less than fat, and on T2-weighted images (T2WI) it is somewhat higher than muscle and equal to or slightly less than fat^[5]. Chemical shift MR imaging is a sensitive method for identifying a microscopic mixture of fat and water; in a patient with a thymus showing CT attenuation values higher than would be expected for fat, chemical shift MR may reveal microscopic fat, thereby excluding a true mass^[6]. In general, when imaging shows a convex margin, focal enlargement of a lobe or multilobularity in an adult^[7], or when the CT attenuation is higher than fat, a mass should be suspected (Fig. 3)^[8].

In infants, the normal thymus is malleable during the respiratory cycle, and change in thymic shape during real time ultrasonography has been reported as a useful sign to differentiate normal thymus from a mass^[1]. Similarly, it has also been suggested that change in thymic shape in adults between inspiratory and expiratory CT imaging may be helpful in distinguishing thymic hyperplasia from a thymic mass (Fig. 4)^[9].

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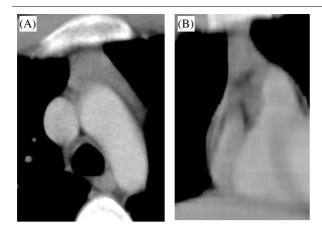


Figure 1 Normal thymus in a 19-year-old. (A) Contrast-enhanced CT demonstrates a bilobed organ, with flat margins. The left lobe is larger than the right, as commonly seen. (B) Coronal reconstruction better demonstrates the triangular thymic shape.

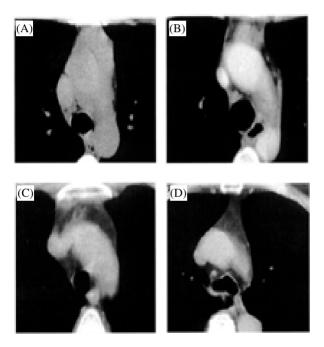


Figure 2 CT images from multiple different patients show the normal involution of the thymus beginning in childhood (A) and progressing through early adulthood (B), middle age (C) and late adulthood (D).

Thymic hyperplasia

There are two types of thymic hyperplasia, lymphoid follicular hyperplasia and true hyperplasia. Lymphoid follicular hyperplasia, also known as autoimmune thymitis, is characterized by normal size and weight of the thymus with chronic inflammation and proliferation of lymphoid follicles, active germinal centers and increased numbers of lymphocytes and epithelial cells^[10]. Follicular hyperplasia is seen in about two-thirds of patients with myasthenia gravis; it may also be associated

with autoimmune diseases or endocrine diseases such as systemic lupus erythematosus, thyrotoxicosis and Addison's disease. In lymphoid follicular hyperplasia, the thymic gland usually retains its normal shape, but it may be either of normal size or enlarged (Fig. 5)^[11], and occasionally there may be a focal mass^[10]. In a patient with myasthenia gravis, enlargement or a focal mass may represent either lymphoid hyperplasia or thymoma.

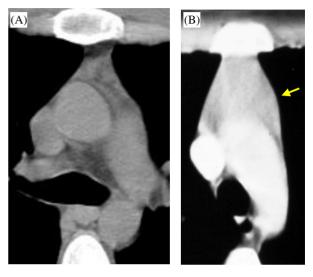


Figure 3 Thymic contour. (A) The normal thymic contour in an adult is biconcave or flat. (B) Convex margin (arrow) suggests thymic abnormality.

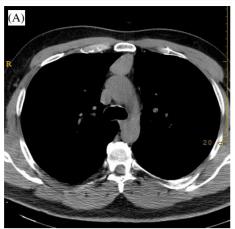
True thymic hyperplasia is much less common than lymphoid follicular hyperplasia and is sometimes seen in association with thyrotoxicosis, Graves' disease, acromegaly and red cell aplasia [10]. True hyperplasia generally manifests as diffuse, symmetric enlargement of the gland, involving both the cortex and the medulla. On imaging studies, the gland is diffusely enlarged and preserves its normal shape, showing a homogenous appearance similar to normal thymic tissue at both CT and MR (Fig. 6) [10].

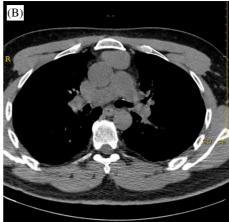
Thymic rebound represents a form of true thymic hyperplasia that may be seen after resolution of a stressful event, for example, after cessation of chemotherapy; this entity is most often encountered in children and young adults (Fig. 7). Thymic rebound must be strongly considered when there is an enlarging anterior mediastinal mass in a patient with lymphoma who has recently completed chemotherapy.

Thymic neoplasms

Thymic epithelial tumors

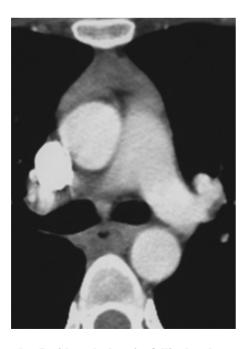
Thymic epithelial tumors originate from the thymic epithelium and are distinct from non-epithelial primary thymic tumors such as lymphomas or germ cell tumors. Thymic epithelial tumors have traditionally been classified into three subgroups including benign thymoma,



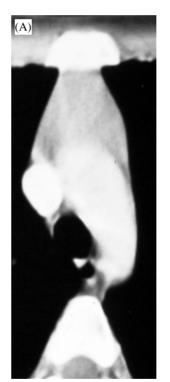


A 53-year-old man showing change in thymic shape between inspiration (A) and expiration (B), considered a sign of benign hyperplasia. Courtesy of Dr Dorith Shaham, Department of Radiology, Hadassah **Hebrew University Medical Center.**

type 1 malignant thymoma (invasive thymoma) and type II malignant thymoma (thymic carcinoma). More recently, however, they have been reclassified according to prognostic implications into thymomas, atypical thymomas and thymic carcinomas [12]. Thymomas tend to show a high degree of organotypical histological differentiation resembling normal thymus; atypical thymomas (sometimes called well-differentiated thymic carcinomas) retain most organotypical features, although they show mild cytological atypia; thymic carcinomas demonstrate loss of organotypical features and abundant cytological atypia.



Incidental thymic follicular hyperplasia in a 36-year-old woman. Minimally enlarged thymus with biconvex margins.



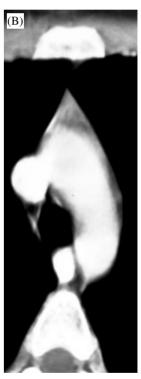
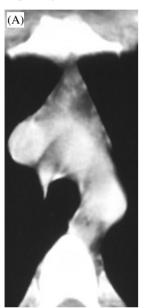


Figure 6 Thymic hyperplasia in a 29-year-old female with Grave's disease. (A) Mild diffuse thymic enlargement with biconvex margins. (B) CT scan 3 years later demonstrates residual normal thymic tissue.

Thymoma

Thymoma is the most common primary tumor in both the thymus and the anterior mediastinum^[13]. These tumors affect men and woman with equal frequency; they are rare in children, and usually present at the age of 50-60^[10,13]. One-third to one-half of patients with thymoma

develop myasthenia gravis; on the other hand, only about 15% of patients with myasthenia gravis develop a thymoma. Approximately 10% of patients with thymoma have hypogammaglobulinemia, and approximately 5%–10% of thymoma patients develop red cell aplasia; conversely, approximately 50% of patients with red cell aplasia develop thymoma [10,14]. Thymomas may also be associated with connective tissue diseases such as systemic lupus erythematosus and rheumatoid arthritis. In addition, almost 20% of patients with thymomas have concomitant malignancy, most commonly lymphoma, lung or thyroid carcinoma (Fig. 8)^[10].



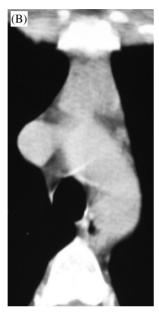


Figure 7 Rebound thymic hyperplasia in a 45-yearold female receiving chemotherapy for melanoma. (A) CT scan performed during chemotherapy shows involuted thymic tissue. (B) Seven months later, after cessation of chemotherapy, there is diffuse homogeneous enlargement of the thymus consistent with rebound thymic hyperplasia.

Most patients with thymoma are asymptomatic from the thymic lesion, and the tumor is detected incidentally on a routine chest radiograph or CT scan obtained for other reasons. If symptoms develop, they may be related to local invasion of the tumor or tumor compression upon adjacent structures; compression upon the central airways may lead to repeated respiratory infections.

Thymomas are classified as invasive or non-invasive, depending on whether or not the tumor capsule is invaded [10]. Only approximately 30% of thymomas are invasive; tumor may spread outside the capsule into adjacent structures such as mediastinal fat, superior vena cava, great vessels, central airways, pleura, pericardium, phrenic nerve, lung or chest wall. Invasive tumors tend to spread along contiguous pleural or pericardial surfaces, usually only on one side of the thorax; leaving behind discrete tumor droplets. Neoplasm may extend into the upper abdomen either via the retrocrural space

or transdiaphragmatically. Lymphogenous metastases are uncommon and hematogenous metastases are rare. Usually thymomas are located in the anterior mediastinum, but they may arise anywhere in the thorax from the neck to the diaphragm. They tend to be slow growing and are variable in size, usually ranging between 5 and 10 cm at the time of diagnosis [13].



Figure 8 Atypical thymoma in a 55-year-old woman with recurrent lung cancer. A homogenous mass with convex margin is demonstrated within the thymus. Left lung nodule (white arrow) represents lung cancer recurrence.

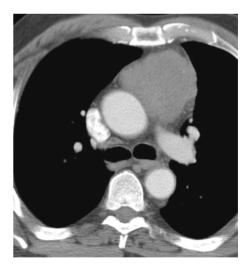


Figure 9 Invasive thymoma. Homogeneous, anterior mediastinal homogeneous mass extends to the left. Irregular interface suggests extracapsular invasion; lung and pericardial invasion were found at surgery.

CT is the modality of choice for evaluation of thymomas. Usually a thymoma appears as a homogeneous, well-defined soft tissue mass that extends to one side of the anterior mediastinum, often draping alongside the heart (Fig. 9). Most thymomas enhance homogeneously, often containing clumps of calcification showing a curvilinear, punctuate or coarse pattern

(Fig. 10). Preservation of surrounding mediastinal fat suggests lack of capsular invasion. In contrast, ill-defined tumor margins, tumor extension across the midline, encasement of vessels and other mediastinal structures, and irregular interfaces with adjacent lung are all suggestive of invasion (Fig. 11). However, contiguity of a thymoma with adjacent structures and loss of intervening fat planes at CT does not necessarily imply tumor invasion [13] (Fig. 12). Small, discrete, nodular tumor implants are commonly seen along the pleural surfaces, and tumor may cross into the upper abdomen, particularly via the retrocrural space (Fig. 13). Pleural effusions are uncommon.



Figure 10 Thymoma in a 35-year-old man with myasthenia gravis, dermatomyositis and hypogam-maglobulinemia. Large mass extending into the right hemithorax, containing punctuate and coarse calcifications. Low attenuation regions suggesting necrosis and/or hemorrhage.

On MR imaging, thymomas tend to exhibit signal characteristics similar to those of normal thymus and usually enhance homogeneously [10]. Heterogeneity, however, may occasionally be seen in cases with cyst formation, hemorrhage or necrosis. The multiplanar capabilities of MRI and helical CT may be helpful in assessing for tumor invasion of adjacent structures [2,13]. FDG avidity may be seen on PET scans in thymomas (Fig. 12)^[15]. However, FDG uptake may also be present in normal thymic tissue in young adults and in cases of thymic hyperplasia, and therefore FDG-PET scanning is not reliable in discriminating among normal thymus, thymic hyperplasia and thymoma^[16]. Potential uses of PET imaging may lie in detection of trans-diaphragmatic spread and distant metastases and in the evaluation for post-operative tumor recurrence (Fig. 14)^[17].

Thymic carcinoma

Thymic carcinomas are uncommon, histologically malignant neoplasms. The most common subtypes are squamous cell carcinoma and lymphoepithelial-like carcinoma, previously classified as atypical thymoma [10,12].

Thymic cancers are biologically aggressive and frequently metastasize hematogenously to lungs, liver, brain and bone. There is a slight male propensity, and the disease typically presents at about the age of $50^{[10]}$. Presenting symptoms are generally secondary to mediastinal compression and/or invasion or related to distant metastases. Patients with this disease have a very poor prognosis; in one study, there was only an 18-month average survival [18] and in another, 5-year survival was approximately 33% [19].

CT generally shows a large, poorly marginated homogeneous or heterogeneous soft tissue mass that appears to invade adjacent structures. Areas of necrosis, hemorrhage, calcification and/or cyst formation may be seen. Pericardial or pleural involvement and pleural effusion are frequent findings (Figs 15 and 16). Hilar lymph node enlargement, diaphragmatic elevation suggesting phrenic nerve palsy and lung nodules suggestive of metastases are findings that should raise the possibility of thymic carcinoma rather than invasive thymoma^[12]. On MR imaging, thymic carcinomas are typically of intermediate signal on T1WI and high signal on T2WI^[10]. It has been suggested that high standardized uptake value (SUV) at PET may differentiate thymic carcinoma from thymoma, thymic hyperplasia and normal thymus^[15,20].

Thymic lymphoma

Hodgkin's disease involves the thymus more commonly than does non-Hodgkin's lymphoma, and the most frequent cell type is nodular sclerosing disease^[2]. About one third of patients with a new diagnosis of Hodgkin's disease have thymic enlargement, either as the primary site of involvement, or due to infiltration from adjacent lymph nodes. Among the non-Hodgkin's lymphomas, large B-cell lymphoma and lymphocytic lymphoma are the most frequent types to occur in the thymus. The thymus may be diffusely enlarged or may have a multinodular appearance, and associated mediastinal lymph node enlargement is frequent (Fig. 17). Although the thymus is usually homogenous in attenuation, heterogeneity, may occasionally be seen due to cystic necrosis or hemorrhage. In addition, cystic changes and calcifications are frequently seen following chemotherapy and radiation therapy [2,10,21].

Thymic carcinoid

Thymic carcinoids arise from cells of neural crest origin (APUD cells), and they are histologically similar to atypical bronchial carcinoids. In 33%–40% of thymic carcinoids, ACTH is secreted, causing ACTH-dependent Cushing syndrome [2]. Other syndromes occasionally associated with thymic carcinoids include multiple endocrine neoplasia syndrome type I or type II and inappropriate secretion of anti diuretic hormone [10].

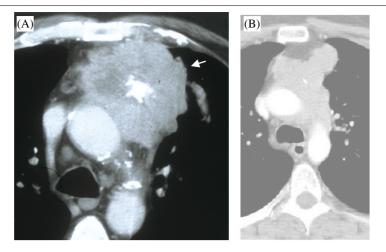


Figure 11 Invasive thymomas. (A) Irregular interface with lung (arrow) suggests pulmonary invasion (surgically proven). (B) Encasement of the aorta and mass protruding into the lung, suggesting invasion.

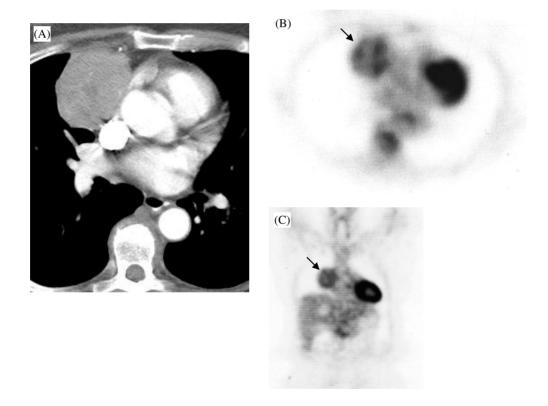


Figure 12 Well-defined anterior mediastinal mass, contiguous with pericardium and heart at CT (A). FDG avid at PET (arrows) (B, C). At surgery, the pericardium was not invaded; microscopic analysis of the resected specimen showed minimal capsular invasion.

These tumors may be locally aggressive and present with signs and symptoms of mediastinal invasion and compression; however, approximately one-third of patients are asymptomatic [10]. Thymic carcinoids are usually malignant, and regional lymph node metastases and/or distant spread of tumor may occur. The tumors tend to recur locally after resection, and patients generally have a poor prognosis. Imaging findings are similar to those of thymoma. Octreotide is a somatostatin analog which is

accumulated by carcinoids and other hormonally active tumors, and octreotide imaging is therefore sometimes useful for detection of occult carcinoids. Octreotide uptake has also been reported in other thymic tumors [2].

Thymolipoma

Thymolipomas are large, benign anterior mediastinal masses containing mature adipose tissue cells and thymic

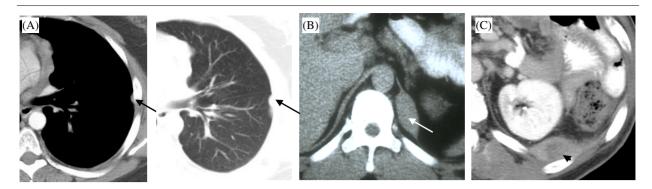


Figure 13 Thymoma tends to spread along the pleural surfaces and may extend into the abdomen via the retrocrural space. (A) Small discrete pleural implant (black arrow), visualized to advantage on lung window. (B) Left retrocrural spread (white arrow). (C) Retroperitoneal implant (black short arrow).

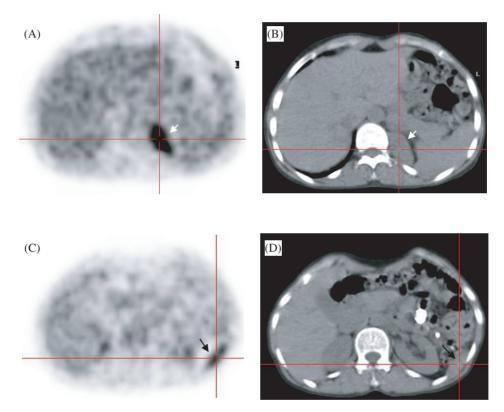
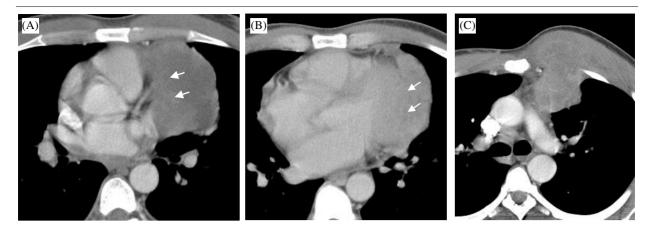


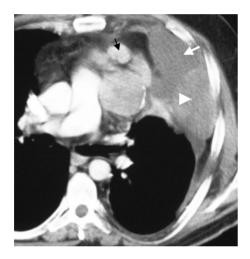
Figure 14 A 35-year-old woman with recurrent thymoma after resection. Combined CT-PET scan shows FDG-avid retroperitoneal implants (arrows). PET images, (A) and (C); CT images, (B) and (D). Courtesy of Dr R. Rubinstein, Department of Nuclear Medicine, Haddassah Hebrew University Medical Center, Jerusalem, Israel.

tissue in varying ratios^[22]. In spite of their large size, they are usually asymptomatic, and surgical excision is curative. There are no known associated immunologic or endocrine disorders. On chest radiographs, mediastinal widening or a large, well-marginated, radiolucent anterior and inferior mediastinal mass is seen. The mass may involve both sides of the mediastinum, or it may be unilateral, draping over the heart and simulating cardiomegaly or diaphragmatic elevation. Deformability of the mass may be evident when imaging in different body positions, probably to the soft, fatty content. The

diagnostic feature of these lesions is the presence of fatty tissue on CT or MR, with variable amounts of soft tissue (Fig. 18(a)). A thymolipoma may diffusely involve the thymus or may appear as a pedunculated mass arising from a normal appearing thymus. The lesion may cause mass effect upon adjacent mediastinal structures. The major entity in the differential diagnosis is a Morgagni hernia containing omentum (Fig. 18(b, c)); a hernia can usually be distinguished by tracing blood vessels within the omental fat down through the diaphragmatic opening into the abdomen.



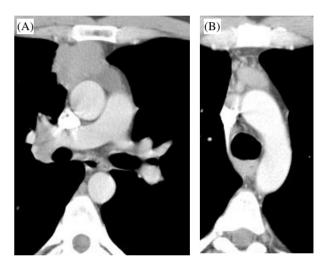
Thymic squamous cell carcinoma in a 40-year-old male. (A, B) Large heterogenous mass extending Figure 15 along the pericardium, with probable invasion (arrows). (C) Six weeks following a Chamberlain procedure (left anterior thoracotomy) there is new chest wall invasion, compatible with tumor seeding in the surgical wound.



High grade thymic carcinoma with mediastinal lymph node enlargement (black arrow) and pleural involvement, including pleural mass (white arrow head) and loculated pleural effusion (white arrow).

Thymic germ cell tumors

The most common location for extragonadal germ cell tumors is within the mediastinum, either within or in the vicinity of the thymus [14,23,24]. Mediastinal germ cell tumors are a heterogeneous group of benign and malignant neoplasms that originate from primitive germ cells, misplaced in the mediastinum during embryogenesis. These tumors are usually seen in adolescents and young adults, and include benign and malignant teratoma, seminoma, embryonal carcinoma, endodermal sinus (yolk sac) tumor, choriocarcinoma, and mixed types. At least 80% are benign, and most of these are teratomas. Benign germ cell tumors are seen equally commonly in males and females; while approximately 90% of malignant germ cell tumors are seen in males.



(A, B) Thymic lymphoma. Thymic mass Figure 17 and enlarged mediastinal and right hilar lymph nodes.

Approximately 60%–70% of mediastinal teratomas are benign, well-differentiated and curable with surgery. Patients are usually asymptomatic, although symptoms from local compression may occur^[14]. Very rarely, proteolytic enzymes from pancreatic or intestinal mucosa within the tumor may precipitate rupture into bronchi, pleura or pericardium[23]. Teratomas generally appear as a well-defined rounded or lobulated mass, often quite large in size and protruding to one side of midline^[14]. The presence of cystic and solid areas is characteristic, typically creating a multilocular cystic appearance; cyst walls may be of variable thickness (Fig. 19). Fatty content and calcifications are common, the latter manifesting on chest radiographs in up to 29% of cases [14]. The combination of soft tissue, cystic areas, fat and calcification on CT is highly suggestive of benign, mature teratoma, although malignant tumors may also show these features (Fig. 20). Malignant teratomas contain foci of carcinoma or sarcoma; these tumors may have more poorly defined margins and more nodular

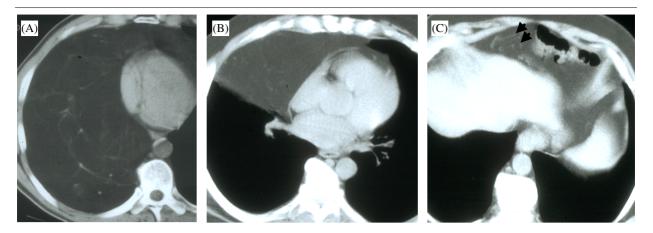
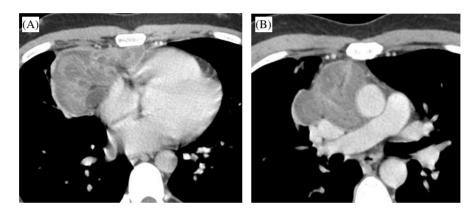
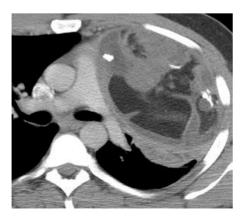


Figure 18 Thymolipoma and thymolipoma mimic. (A) Thymolipoma manifesting as a large fatty mass containing small amounts of soft tissue, filling the entire right hemithorax. (B, C) Morgagni hernia containing omental fat, simulating thymolipoma. Mesenteric vessels (arrowheads) can be tracked into the hernia, suggesting the correct diagnosis.



Mature, benign teratoma in a 35-year-old male presenting with chest pain. (A) Anterior mediastinal heterogeneous mass, containing cystic and enhancing solid areas. (B) The mass appears to encase adjacent mediastinal structures with no apparent separating fat plane. However, at surgery there was no invasion of these structures and complete resection was achieved.

soft tissue components compared to benign teratomas (Fig. 21).

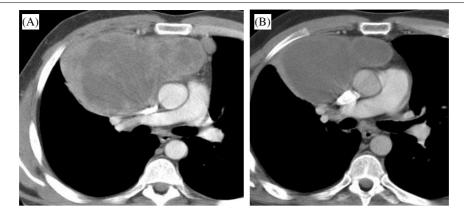


A 43-year-old male with primary malignant mediastinal germ cell tumor demonstrating both fatty content and dense calcification.

Mediastinal seminomas are malignant neoplasms of a single histological cell type that tend to occur in Caucasian men in the third and fourth decade of life^[14]. They manifest radiologically as a bulky, lobulated, homogenous mass. Calcification and local invasion are rare, although metastases to regional lymph nodes and bones may be seen. Malignant mediastinal nonseminomatous germ cell tumors may be associated with hematological malignancies or Klinefelter's syndrome^[14]. These tumors tend to manifest radiologically as large, irregular masses, often containing heterogeneous areas of necrosis, hemorrhage and cyst formation. Pleural and pericardial effusions are common. Local invasion to adjacent structures, including chest wall, and locoregional and distant metastases may occur.

Thymic cysts

Thymic cysts account for about 3% of anterior mediastinal masses [25]. Congenital cysts are rare unilocular



A 38-year-old male with primary malignant mediastinal germ cell tumor. (A) At presentation the mass contained both soft tissue and cystic areas. (B) Following chemotherapy, the mass became predominantly cystic. Subsequent resection revealed no viable tumor.

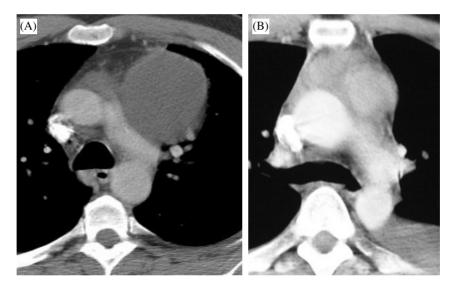


Figure 22 (A) A 45-year-old male with chest pain and a simple appearing cyst in the region of the thymus; histological analysis of the resected mediastinal lesion demonstrated a bronchogenic cyst. (B) A 31-year-old male with pleuritic chest pain. A high attenuation rounded thymic mass was resected and found to be a benign hemorrhagic cyst.

lesions arising from the thyomopharyngeal duct and are usually asymptomatic and discovered incidentally [21]. Acquired lesions are usually multilocular; they may be secondary to radiation therapy for Hodgkin's disease or may be seen in non-radiated thymic neoplasms such as thymoma, lymphoma or seminoma, or even after thoracotomy^[10,21,25]. Inflammatory cysts may occur in patients with autoimmune diseases including Sjogren's syndrome, systemic lupus erythematosus, aplastic anemia, myasthenia gravis, although most such lesions are of unknown etiology. Multilocular benign thymic cysts have occasionally been observed in patients with AIDS, probably representing a manifestation of the diffuse, infiltrative lymphocytosis syndrome ^[26].

Thymic cysts may show fluid attenuation at CT or they may be higher in density, depending on the contents (Fig. 22). The presence of a clearly definable wall or wall calcification has been reported to favor the diagnosis of secondary cyst over congenital cyst^[25]. A soft tissue mass within the cyst does not necessarily represent a thymic neoplasm; benign tissue may cause this finding^[25]. MR imaging may be useful to differentiate hemorrhagic fluid from soft tissue. Typically the cysts will show low signal intensity on T1WI and high signal intensity on T2WI. However, if the cyst contains proteinaceous material, it may exhibit high signal intensity on both T1WI and T2WI^[10].

Conclusions

Imaging evaluation of the thymus is challenging because thymic size, shape and consistency change with age, and there is a moderate degree of normal variation in glandular appearance between individuals. Knowledge of the normal spectrum of thymic appearances is important to prevent overdiagnosing or underdiagnosing thymic lesions. Many different types of disorders may affect the thymus, and imaging findings may be non-specific. Familiarity with different manifestations of disease entities involving the gland helps reach the correct diagnosis or, at the very least, narrow the differential diagnosis. While CT is the first line imaging tool, other imaging modalities may provide additional valuable structural or functional information. Appropriate use of imaging coupled with review of relevant clinical information regarding the patient are important to reach an accurate diagnosis.

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